On pages 7-8, please delete paragraph 0018 and, insert the following replacement paragraph 0018. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0018] If the nucleotide sequence is random, the probability that a sequence of given length translated from it will have a particular amino acid sequence can be calculated simply by multiplying together the frequencies in the genetic code of the codons encoding each amino acid [amino acid] in the sequence. Since some amino acids have as many as six codons and others as few as one, the predicted frequency will vary depending on the amino acid sequence itself. Thus the sequence LRRLLR (SEQ ID NO: 1), made up entirely of six-codon amino acids, will appear at a frequency of 1 in $(6/61)^6$, or approximately once in a million codons, and the sequence MWWMMW (SEQ ID NO: 2), made up entirely of one-codon amino acids, will appear at a frequency of 1 in $(1/61)^6$, or approximately once in fifty billion codons. The frequencies of other sequences will fall between these two extremes. The important point for us is that even a relatively short sequence will appear very rarely, and so if we can determine the amino acid sequence of a peptide translated from unknown sequence, we can match it to a portion of the reference sequence with high specificity.

On page 15, please delete paragraph 0031 and, insert the following replacement paragraph 0031. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0031] Comparison of the experimental results with the values in the table indicates reveals a match to the predicted mass value for one of the ten candidates – specifically the sequence that begins at position 3190 of the reference sequence and proceeds from right to

left. Retrieval of the reference sequence beginning at position 3190 indicates that the cloned sequence begins with "GAATTCTTACACCTCATACTTTCCCAAGCCCCAACTTTCTCATCT GAAAATGGTAATAGTATCATCCTTACATGTTTAAGGTCATGAATTGCTAT GTGTA.....(1st 100 nucleotides shown) (SEQ ID NO: 3). The identification is confirmed by dideoxy sequencing from a primer 150 nucleotides upstream of the junction between the pUC19 sequence and the EcoRI fragment.

On page 15, please delete paragraph 0033 and, insert the following replacement paragraph 0033. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0033] The peptide TMITPSLHACRSTLED (SEQ ID NO: 4), representing the N-terminal 16 amino acids of the alpha-complementing factor of beta-galactosidase encoded in pUC19 (and also representing the 16 constant N-terminal amino acids in all of the peptides described in Example 1 above) is used to raise a polyclonal rabbit antibody using standard procedures.

On page 15, please delete paragraph 0034 and, insert the following replacement paragraph 0034. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0034] The mass spectrum of the immunoprecipitate from the induced cell lysate of the clone under examination is observed to contain a distinct peak, at a position corresponding to a mass of 8485±3 Daltons, that is not observed in the control. Comparison of the experimental results with the values in the table in example 1 above indicates that the insert begins at position 9241 of the reference sequence and proceeds from left to right in the Genbank

sequence. Retrieval of the reference sequence beginning at position 9241 indicates that the cloned sequence begins with

GAATTCACATAAATCGCAAATTTTTTTTTCCTTCCCAGAGCC

ATCCAAAACTCTGTTTGTCAAAGGCCTGTCTGAGGATACCACTGAAGAGA

CATTAAAG.....(1st 100 nucleotides shown) (SEQ ID NO: 5). The identification is confirmed by dideoxy sequencing as described in Example 1.

On pages 16-17, please delete paragraph 0038 and, insert the following replacement paragraph 0038. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0038] To identify the nucleotide sequence adjacent to the pTriplEx' vector, each EcoRI site in the JO5584 sequence is identified and ligated, in silico, to the EcoRI site in the pTriplEx' vector. For each such in silico construct, the amino acid sequences of the two expected hybrid translation products (from each of the start codons in the vector to the first in frame stop codons encountered in the insert) are calculated. The mass of each peptide is calculated and all 10 peptide pairs are tabulated, as shown in the table below. Comparison of the experimental results (i.e., peptides of 4255 and 2635 Da.) with the values predicted in the table indicates that the insert begins at position 4028 of the reference sequence and proceeds in the forward direction.

It is concluded that the 5' end of the sequence joined to the vector is

GAATTCTCTTGGGTT TTGTGGTGTGCTAGACTTAATTACCCATGAATGATTT

TGTCCTCTTGAGAAAATTTCAATAGCACATCTATTAGTGTTTTTTAT....(1st 100 nucleotides shown) (SEQ ID NO: 6). The identification is confirmed by dideoxy sequencing from the plasmid using a primer 150 nucleotides 3' to the pTriplEx' EcoRI site.

Position of EcoRI site	Orientation in pTriplEx'	Start Codon	Predicted Peptide Mass	
3190	forward		1st	6137
3190	forward		2nd	5707
3190	reverse	1st	6278	
3190	reverse	2nd	3891	
4208	forward		1st	4255
4208	forward		2nd	2635
4208	reverse	1st	19748	
4208	reverse	2nd	3905	
6066	forward		1st	3595
6066	forward		2nd	3606
6066	reverse	1st	6401	
6066	reverse	2nd	1363	
9241	forward		1st	3583
9241	forward		2nd	7122
9241	reverse	1st	4582	
9241	reverse	2nd	1746	
9543	forward		1st	5306
9543	forward		2nd	1477
9543	reverse	1st	9906	
9543	reverse	2nd	2516	

On page 19, please delete paragraph 0040 and, insert the following replacement paragraph 0040. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0040] Two oligonucleotide primers are synthesized using standard methods. In one, CCCGAATTCAGCAGGTAAAAATCAAGG (SEQ ID NO: 7), the first 10 nucleotides contain an EcoRI site (underlined) and last 17 nucleotides correspond to the first 17 nucleotides of exon 2 of the human nucleolin gene. The other, GGGGAATTCTTACTCTTCTCCACTGCTAT (SEQ ID NO: 8), the last 17 nucleotides correspond to the reverse complement of the last 17 nucleotides of exon 2, followed immediately (in the sense orientation of the oligonucleotide) by the stop codon TAA and a sequence that includes an EcoRI site (underlined).

On pages 21-24, please delete paragraph 0046 and, insert the following replacement paragraph 0046. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0046] The program was run with the 24 nucleotide input sequence CAACTAGAAGAGGTAAGAAACTAT (SEQ ID NO: 9). Two reading frames were selected; the forward reading frame beginning with the first nucleotide (F1) and the reverse (antisense) reading frame beginning with the second antisense nucleotide (R2). The results are shown below.

[begin]

Enter Sequence:

[input] CAACTAGAAGAGGTAAGAAACTAT (SEQ ID NO: 9)

[output] Protein: QLEEVRNY (SEQ ID NO: 10)

Which reading frames would you like to examine?

1: Forward (F1)

2: Forward; first base removed (F2)

3: Forward; second base removed (F2)

4: Reverse (R1)

5: Reverse first base removed (R2)

6: Reverse second removed (R3)

[input] 1,5

[output] **MASS DIFFERENCES**

Location	Mutation	Frame F1	Frame R2
	None	1032.13	722.89
	/A(K)	0.04	0.00
1	C-{ G(E)	0.99	0.00
	\T(Z)	-1032.13	0.00
	/G(R)	28.06	0.00
2	(Q) A-{ T(L)	-14.97	0.00
	\C(P)	-31.01	0.00
	/G(Q)	0.00	0.00
3	A-{ T(H)	9.01	0.00
	\C(H)	9.01	0.00
	/A(I)	0.00	276.34
4	C-{ G(V)	-14.03	276.34
	\T(L)	0.00	0.00
	/C(P)	-16.04	299.37

5	(L) T-{ A(Q)	14.97	226.32	
	\G(R)	43.03	200.24	
	/G(L)	0.00	241.29	
6	A-{ T(L)	0.00	241.33	
	\C(L)	0.00	242.28	
	/T(Z)	-790.84	-34.02	
7	G-{ C(Q)	-0.99	-34.02	
	\A(K)	-0.95	0.00	
	/G(G)	-72.07	-60.10	
8	(E) A-{ T(V)	-29.99	16.00	
	\C(A)	-58.04	-44.04	
	/G(E)	0.00	-34.02	
9	A-{ T(D)	-14.03	-34.02	
	\C(D)	-14.03	-48.05	
	/T(Z)	-661.72	0.00	
10	G-{ C(Q)	-0.99	0.00	
	\A(K)	-0.95	0.00	
	/G(G)	-72.07	-16.04	
11	(E) A-{ T(V)	-29.99	23.98	
	\C(A)	-58.04	43.03	
	/T(D)	-14.03	0.00	
12	G-{ C(D)	-14.03	-14.03	

	\A(E)	0.00	34.02
	/T(L)	14.03	-423.52
13	G-{ C(L)	14.03	-423.52
	\A(I)	14.03	0.00
	/C(A)	-28.05	-60.04
14	(V) T-{ A(E)	29.99	-16.00
	\G(G)	-42.08	-76.10
	/G(V)	0.00	-26.04
15	A-{ T(V)	0.00	-49.08
	\C(V)	0.00	-48.09
	/G(G)	-99.14	0.00
16	A-{ T(Z)	-433.47	0.00
	\C(R)	0.00	0.00
	/T(I)	-43.03	76.10
17	(R) G-{ C(T)	-55.09	16.06
	\A(K)	-28.02	60.10
	/G(R)	0.00	10.04
18	A-{ T(S)	-69.11	14.02
	\C(S)	-69.11	-16.00
	/G(D)	0.99	0.00
19	A-{ T(Y)	49.08	0.00

	\C(H)	23.04	0.00
	/G(S)	-27.02	-28.05
20	(N) A-{ T(I)	-0.94	15.96
	\C(T)	-13.00	-42.08
	/A(K)	14.07	48.05
21	C-{ G(K)	14.07	14.03
	\T(N)	0.00	14.03
	/C(H)	-26.04	18.03
	\G(D)	-49.08	0.00
22	T-{ A(N)	-48.09	0.00
	/G(C)	-60.04	-12.06
23	(Y) A-{ T(F)	-16.00	15.01
	\C(S)	-76.10	43.03
	/C(Y)	0.00	-14.03
24	T-{ A(Z)	-163.18	0.00
	\G(Z)	-163.18	0.00

Enter the detection threshold:

[input] 0.8 Dalton.

[output] Undetectable amino acid substitutions: 1.(Q)C-A(K)

On pages 26, please delete paragraph 0049 and, insert the following replacement paragraph 0049. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0049] Two primers, of sequences GGCCCGGAATTCTCCAGCTGTCTGTTTCCCTTTAAG (SEQ ID NO: 12) and AATTTACTCGAGCTACCCCCAGCTGCCCAGGGCCTAC (SEQ ID NO: 13) were synthesized and used to PCR amplify rds/peripherin exon 2 from an individual known to carry a wild type allele of rds/peripherin. The amplicon was cut with EcoRI and XhoI and cloned into the EcoRI/XhoI sites of the pGEX derivative described in Nelson et al. The resulting plasmid was cut with Xho 1, treated with Klenow fragment of DNA polymerase, and self-ligated to produce a construct expected to produce a fusion protein with the sequence shown below.

MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLE
FPNLPYYIDGDVKLTQSMAIIRYIADKHNMLGGCPKERAEISMLEGAVLDIRYGVSRIAYSK
DFETLKVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLD
AFPKLVCFKKRIEAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLIEGRGIQDLVPH
TTPHHTTPHHTTPHHTTPQDLNSPAVCFPLSRIKSNVDGRYLVDGVPFSCCNPSSPRPCIQY
QITNNSAHYSYDHQTEELNLWVRGCRAALLSYYSSLMNSMGVVTLLIWLFEVGPGQLGV
ARSSGRIVTD (SEQ ID NO: 14)

On page 26, please delete paragraph 0050 and, insert the following replacement paragraph 0050. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0050] The sequence of exon 2 of the human rds/peripherin gene (Genbank accession M73531) is shown below. Intron sequence is shown in lower case; exon sequence in upper case.

gggaagcccatctccagctgtctgtttcccttaagTCGAATCAAGAGCAACGTGGATGGGCGGTACCTGGT
GGACGGCGTCCCTTTCAGCTGCTGCAATCCTAGCTCGCCACGGCCCTGCATCCAGTAT
CAGATCACCAACAACTCAGCACACTACAGTTACGACCACCAGACGGAGGAGCTCAAC
CTGTGGGTGCGTGGCTGCAGGGCTGCCCTGCTGAGCTACTACAGCAGCCTCATGAACT
CCATGGGTGTCGTCACGCTCCTCATTTGGCTCTTCGAGgtaggccctgggcagctgggggtagagggtaa
ggagagcctcc (SEQ ID NO: 11)

On page 27, please delete paragraph 0055 and, insert the following replacement paragraph 0055. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0055] The amplicons described in the previous example are reamplified using the upstream primer

5'GGATCCTAATACGACTCACTATAGGGAGACCACCATGCATCACCATCATCACCATCA
CCACTCTCCAGCTGTCTGTTTCCCTTTAAG (SEQ ID NO: 15) and the downstream primer

5' CTTAGTCATTATACCCCCAGCTGCCCAGGGCCTAC (SEQ ID NO: 16). The upstream primer contains a T7 promoter followed by a translation initiation sequence (start codon underlined) followed by a sequence encoding eight histidines followed by sequence identical to the red/peripherin sequence immediately 5' to rds/peripherin exon 2. The downstream primer contains two stop codons (in antisense orientation) preceding the sequence complimentary to the sequence just 3' to red/peripherin exon 2.

On pages 28-28, please delete paragraph 0061 and, insert the following replacement paragraph 0061. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0061] Leukocyte DNA from 5 individuals is PCR amplified using Taq polymerase by the primers shown below that hybridize at the 5' and 3' ends of intron 2 of the human CFTR gene (REF). The forward primers are identical over their 3' 22 nucleotides (which correspond to the 22 nucleotides immediately 5' to exon 2), but differ at their 5' ends as shown in underlined type.

PCR primers used to amplify CFTR exon 2.

	5' (forward) primer	3' (reverse) primer
Individual 1	ttcctcctctctttattttag (SEQ ID NO: 17)	actaaacaatgtacatgaacatac (SEQ ID NO: 18)
Individual 2	tatttcctcctctctttattttag (SEQ ID NO. 19)	actaaacaatgtacatgaacatac (SEQ ID NO: 20)
Individual 3	tattacttcctcctctctttattttag (SEQ ID NO. 21)	actaaacaatgtacatgaacatac (SEQ ID NO: 22)
Individual 4	tactatttattcctcctctctttattttag (SEQ ID NO: 23)	actaaacaatgtacatgaacatac (SEQ ID NO: 24)
Individual 5	tactatttatacttcctcctctctttattttag (SEQ ID NO: 25)	actaaacaatgtacatgaacatac (SEQ ID NO: 26)

On page 29, please delete paragraph 0062 and, insert the following replacement paragraph 0062. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0062] The primers used for individual 1 amplify a DNA of the sequence shown below. (The exon 2 sequence is shown in bold type.)

ttcctcctctctttattttagCTGGACCAGACCAATTTTGAGGAAAGGATACAGACAGCGCCTGGAA

TTGTCAGACATATACCAAATCCCTTCTGTTGATTCTGCTGACAATCTATCTGAAAAATT

GGAAAGgtatgttcatgtacattgtttagt (SEQ ID NO: 27)

On page 33, please delete paragraph 0072 and, insert the following replacement paragraph 0072. Pursuant to 37 C.F.R. § 1.121, the following is a clean copy of the replacement paragraph. A marked-up copy of the replacement paragraph is attached on separate sheets.

[0072] Exon 7 is 247 nucleotides in length, and so there are 741 (247 x 3) possible single nucleotide substitutions in the exon. The sequence of exon 7 is shown below. The first complete codon in the sequence begins with the second A in the sequence.

AACAGAACTGAAACTGACTCGGAAGGCAGCCTATGTGAGATACTTCAA

TAGCTCAGCCTTCTTCTTCTCAGGGTTCTTTGTGGTGTTTTTATCTGTGCTTCCCTATGC

ACTAATCAAAGGAATCATCCTCCGGAAAATATTCACCACCATCTCATTCTGCATTGTT

CTGCGCATGGCGGTCACTCGGCAATTTCCCTGGGCTGTACAAACATGGTATGACTCTC

TTGGAGCAATAAACAAAATACAG (SEQ ID NO: 28)